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L10	L9 same l7	2	L10
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L8	L7 with l3	7	L8
L7	L6 with l2	403	L7
L6	L5 or l4	379050	L6
L5	enzymatic	109750	L5
L4	cleavage or enzyme or cleaved	361669	L4
L3	muta$	142521	L3
L2	factor VII	2598	L2
L1	factor V	3261	L1

END OF SEARCH HISTORY

First Hit Fwd Refs Previous Doc Next Doc Go to Doc#
End of Result Set

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L10: Entry 2 of 2 File: USPT Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6210929 B1
TITLE: Fusion protein comprising a furin derivative or a derivative of a furin analogue and a heterologous sequence

Brief Summary Text (8):
Among the further proproteins which are cleaved by furin or by subtilisin-like enzymes, respectively, are a series of hormones and growth factors (e.g., proactivin A, hepatocyte-growth factor), plasma proteins (albumin, factor VII, factor IX, factor X), receptors (insulin pro-receptor), viral proteins (e.g. HIV-1 gp160, influenza virus haemagglutinin) as well as bacterial proteins (diphteria toxin, anthrax toxin) (Decroly et al., J. Biol. Chem. 269:12240-12247, 1994, Stieneke-Grober et al., EMBO J. 11:2407-2414, 1992, Barr, Cell 66:1-3, 1991, Wasley et al., J. Biol. Chem. 268:8458-8465, 1993, Klimpel et al., Proc. Natl. Acad. Sci. USA 89:10277-10281, 1992, Tsuneoka et al., J. Biol. Chem. 268:26461-26465, 1993, Bresnahan et al., J. Cell. Biol. 111:2851-2859, 1990, Hosaka et al., J. Biol. Chem. 266:12127-12130, 1991, Vey et al., J. Cell. Biol. 127:1829-1842, 1994).

Previous Doc Next Doc Go to Doc#

L8: Entry 3 of 7 File: USPT Oct 20, 1998

DOCUMENT-IDENTIFIER: US 5824639 A
TITLE: Modified factor VII anticoagulant proteins

Detailed Description Text (30):
To generate the Arg.sub.152 .fwdarw.Glu Factor VII (R152E Factor VII) activation cleavage site mutant, the vector pUC119 (Vieira and Messing, Meth. Enzymol. 153: 3-11 (1987)) was first modified using oligonucleotide adapters to insert an Nco I cleavage site between the Xba I and Bam HI sites in the polylinker sequences. This manipulation and subsequent steps described below were performed according to standard protocols (Maniatis et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor (1982)). Six oligonucleotides (see Table 2) comprising the Factor VII cDNA sequences between the Xba I site at 562 basepairs (bp) and the Nco I site at 635 bp (FIG. 2a) were then ligated into this pUC119-derived vector (FIG. 2b). The oligonucleotides encoded a sequence identical to that of native Factor VII except for the substitution of a glutamic acid for arginine at amino acid 152.

L8: Entry 3 of 7 File: USPT Oct 20, 1998

US-PAT-NO: 5824639
DOCUMENT-IDENTIFIER: US 5824639 A

TITLE: Modified factor VII anticoagulant proteins

DATE-ISSUED: October 20, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Berkner; Kathleen L.	Seattle	WA		

US-CL-CURRENT: 514/12; 424/94.64, 435/212, 435/226, 530/384

CLAIMS:

What is claimed is:

1. A composition comprising Factor VII having at least one amino acid substitution or deletion modification in the activation cleavage site of the activation region wherein said Factor VII is resistant to activation by Factor Xa and inhibits the clotting activity of wild-type Factor VIIa.

2. The composition according to claim 1, wherein the Factor VII is human.

3. The composition according to claim 1, wherein the Factor VII is bovine.

4. The composition according to claim 1, wherein the activation cleavage site of said activation region is modified by an amino acid substitution.

5. The composition according to claim 1, wherein the modification in the activation cleavage site comprises an amino acid substitution within an Arg-Ile dipeptide.

6. The composition according to claim 5, wherein the Arg of the Arg--Ile dipeptide is substituted with another amino acid.

7. The composition according to claim 6, wherein Glu, Leu, Asp, Gly, or Ile is substituted for Arg.

8. The composition according to claim 5, wherein the Ile of the Arg--Ile dipeptide is substituted with a different amino acid.

9. A composition comprising Factor VII having a single amino acid substitution or deletion in the activation region wherein said Factor VII is resistant to activation by Factor Xa and inhibits the clotting activity of wild-type Factor VII.

10. The composition according to claim 9, wherein Glu, Leu, Asp, Gly, or Ile is substituted for the Arg residue of an Arg-Ile dipeptide.

11. The composition according to claim 1, wherein the modified Factor VII is resistant to activation by Factor IXa.

12. The composition according to claim 1, wherein the modified Factor VII is substantially pure.

13. The composition according to claim 1, wherein the Factor VII having at least one amino acid modification binds tissue factor.

14. The composition according to claim 13, wherein the modified Factor VII competes with wild-type Factor VIIa for binding to tissue factor.

15. A method of treating a patient for a coagulation-related disorder, said method comprising administering to said patient a therapeutically effective dose of a composition comprising Factor VII having at least one amino acid substitution or deletion modification in the activation cleavage site of the activation region wherein said Factor VII is resistant to activation by Factor Xa and inhibits the clotting activity of wild-type Factor VIIa.

16. The method according to claim 15, wherein the Factor VII composition administered to the patient is human.

17. The method according to claim 16, wherein the modification of the activation region comprises an amino acid substitution within an Arg-Ile dipeptide.

18. The method according to claim 17, wherein the Arg of the Arg--Ile dipeptide is substituted with another amino acid.

19. The method according to claim 18, wherein Glu, Leu, Asp, Gly, or Ile is substituted for Arg.

20. The method according to claim 15, wherein the modified Factor VII competes with wild-type Factor VIIa for binding to tissue factor.

21. A method of inhibiting coagulation in a patient comprising administering to said patient a dose sufficient to effectively inhibit coagulation of a composition comprising Factor VII having at least one amino acid substitution or deletion modification in the activation cleavage site of the activation region wherein said Factor VII is resistant to activation by Factor Xa and inhibits the clotting activity of wild-type Factor VIIa.

22. A pharmaceutical composition comprising a modified Factor VII according to any of claims 1, 3, 8, 9, 10, 12 or 14 and a physiologically acceptable carrier.

Previous Doc Next Doc Go to Doc#

L8: Entry 4 of 7 File: USPT Apr 14, 1998

DOCUMENT-IDENTIFIER: US 5739101 A
TITLE: Tissue factor mutants useful for the treatment of myocardial infarction and coagulopathic disorders

Detailed Description Text (5):
The term "tissue factor protein mutant" is defined as a polypeptide having at least qualitative biological activity in common with the polypeptide of FIG. 1 (SEQ ID NO:1). The qualitating biological activity referred to is the capacity to neutralize the ability of tissue factor to induce blood coagulation. By "capable of neutralizing the ability of tissue factor to induce coagulation" is meant inhibiting any available tissue factor, from whatever source, from inducing blood coagulation through the extrinsic coagulation pathway(see e.g. Bach, R., CRC Crit. Rev Biochem. 23: 339-368 (1988)). Without intending to be limited to any particular theory or mechanism, the following brief explanation is provided to aid in the understanding of how a tissue factor mutant can be capable of inhibiting coagulation. It is believed that by mutating certain amino acid residues of tissue factor protein, a "mutant confomer cofactor" is produced that is capable of binding to the enzyme factor VII/VIIa, but the "mutant confomer cofactor"-enzyme complex so formed is incapable of catalyzing the conversion of substrate (factor X) to product (factor Xa). Thus the tissue factor protein mutant of the instant invention is believed to compete with any wild-type tissue factor for the cofactor binding site on factor VII/VIIa, thereby neutralizing or preventing the tissue factor from acting as a cofactor in the coagulation cascade. As will be appreciated from the foregoing, the term inhibit or neutralize is a relative term. Thus the terms neutralize or inhibit when used to describe the biological activity of the instant tissue factor protein mutant means a mutant that when added in a 10-fold molar excess to wild-type tissue factor in a standard chromogenic assay (see e.g. Roy, S., J. Biol. Chem. 266: 4665-4668 (1991) and O'Brien, D., et al., J. Clin. Invest., 82: 206-212 [1988]) produces at least a 50% inhibition of the conversion of factor X to Xa in the presence of factor VII and other necessary reagents. Preferably the tissue factor protein mutant will produce at least a 50% inhibition at a 5-fold molar excess and most preferably at a 2-fold molar excess. The very most preferred tissue factor protein mutant will produce at least 50% inhibition of the conversion of factor X to Xa when present in a 1:1 stoichiometric ratio with wild type tissue factor protein.

Detailed Description Text (32):
The inactive TF mutant K165A, K166A transiently expressed on the cell surface was found to bind factor VII (FIG. 5A) and to compete for factor VII with wild-type TF in a relipidation assay (FIG. 5B) where 50% inhibition of wild-type TF activity was seen when wild-type and mutant TF were present at a 1:1 stoichiometric ratio. Moreover, factor VII when bound to cells expressing the K165A, K166A TF double mutant, although functionally inactive, underwent a similar cleavage to a two-chain disulfide linked form as was seen with factor VII bound to cells expressing wild-type TF. A similar cleavage has previously been shown to be due to intrinsic factor Xa activity (Fair, D. S., & MacDonald, M. J., J. Biol. Chem., 262: 11692-11698).